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1

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| APPLICATION NO.   | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|-------------|----------------------|---------------------|------------------|
| 10/791,093  | 03/01/2004  | John Bryan Jones     | M-9066 US           | 2461             |
| <div>24251      7590      09/27/2007</div> <div>SKJERVEN MORRILL LLP</div> <div>25 METRO DRIVE</div> <div>SUITE 700</div> <div>SAN JOSE, CA 95110</div> |             |                      |                     |                  |
|   |             |                      | EXAMINER            |                  |
|   |             |                      | MOORE, WILLIAM W    |                  |
|   |             |                      | ART UNIT            | PAPER NUMBER     |
|   |             |                      | 1656                |                  |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

|                              |                        |                     |  |
|------------------------------|------------------------|---------------------|--|
| <b>Office Action Summary</b> | <b>Application No.</b> | <b>Applicant(s)</b> |  |
|                              | 10/791,093             | JONES ET AL.        |  |
|                              | <b>Examiner</b>        | <b>Art Unit</b>     |  |
|                              | William W. Moore       | 1656                |  |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-62 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☐ Claim(s) \_\_\_\_ is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☒ Claim(s) 1-62 are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____                                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date ____   | 6) <input type="checkbox"/> Other: ____                           |

## DETAILED ACTION

*Election/Restrictions*

Restriction to one of the following inventions is required under 35 U.S.C. § 121:

- I-III. Claims 1-20, drawn to multiple inventions including three classes of cysteine-modified hydrolases: (I)  $\alpha/\beta$  serine hydrolases, (II) subtilisins, and (III) chymotrypsins, classified in class 435, and, respectively, subclasses 212, 219, and 226.
- IV-VI. Claims 21-30, drawn to multiple inventions of methods of using cysteine-modified (I)  $\alpha/\beta$  serine hydrolases, (II) subtilisins, and (III) chymotrypsins to form a covalent bond between an ester and a primary amine, classified in class 435, subclass 128.
- VII-IX. Claims 31-37, drawn to multiple inventions of methods of using cysteine-modified (I)  $\alpha/\beta$  serine hydrolases, (II) subtilisins, and (III) chymotrypsins and an acyl donor to resolve a mixture of racemic primary and secondary alcohols by transesterification, classified in class 435, subclass 233.
- X-XII. Claims 38-42, drawn to multiple inventions of methods of using cysteine-modified (I)  $\alpha/\beta$  serine hydrolases, (II) subtilisins, and (III) chymotrypsins to form a covalent bond between a chiral compound and a substrate by any one of a transamidation, transesterification, or transpeptidation reaction, classified in class 435, subclass 193.
- XIII-XV. Claims 43-50, drawn to multiple inventions of methods of using cysteine-modified (I)  $\alpha/\beta$  serine hydrolases, (II) subtilisins, and (III) chymotrypsins to lengthen a polypeptide by forming a peptide bond between an amino acid ester at the carboxyl terminus of a polypeptide with the primary amine of an amino acid, classified in class 435, subclass 68.1.
- XVI.-XVIII. Claims 51-62, drawn to multiple inventions of methods of using cysteine-modified (I)  $\alpha/\beta$  serine hydrolases, (II) subtilisins, and (III) chymotrypsins capable of conducting any of a transamidation, transesterification, or transpeptidation reaction comprising selecting one or more amino acid positions in a subsite region mediating substrate binding for replacement with a cysteine, recombinantly producing a (I)  $\alpha/\beta$  serine hydrolase, (II) a subtilisin, or a (III) chymotrypsin having at least one cysteine replacement in at least one substrate binding site region, and forming a covalent bond between the thiol group of the cysteine and a non-peptide chemical compound, classified in class 435, subclass 69.1.

The Inventions of Groups I-III are directed to related products. The related inventions are distinct if (1) if the inventions as claimed are **either** not capable of use together **or** can have a materially different design, mode of operation, function, or different effect; (2) the inventions do not overlap in scope, i.e., they are mutually exclusive, and (3) the inventions as claimed are not

Art Unit: 1656

obvious variants, and (3). See MPEP § 806.05(j). In the instant case (1) the inventions of the hydrolases of Groups I-III, as claimed, are different compositions of matter that have materially different designs and effects. Furthermore, the inventions as claimed do not encompass overlapping subject matter, particularly where they are differently classified, and there is nothing of record to show them to be obvious variants.

Inventions of Groups I-III and Groups IV-VI are related as products and processes of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the processes for using the products as claimed can be practiced with other, materially different, products or (2) the products as claimed can be used in materially different processes of using the products. See MPEP § 806.05(h). In the instant case the products as claimed can be used in materially different processes of using the products, such as methods of the inventions of Groups VII-IX.

Inventions of Groups I-III and Groups VII-IX are related as products and processes of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the processes for using the products as claimed can be practiced with other, materially different, products or (2) the products as claimed can be used in materially different processes of using the products. See MPEP § 806.05(h). In the instant case the products as claimed can be used in materially different processes of using the products, such as methods of the inventions of Groups X-XII.

Inventions of Groups I-III and Groups X-XII are related as products and processes of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the processes for using the products as claimed can be practiced with other, materially different, products or (2) the products as claimed can be used in materially different processes of using the products. See MPEP § 806.05(h). In the instant case the products as claimed can be used in materially different processes of using the products, such as methods of the inventions of Groups XIII-XV.

Inventions of Groups I-III and Groups XIII-XV are related as products and processes of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the processes for using the products as claimed can be practiced with other, materially different, products or (2) the products as claimed can be used in materially different processes of using the products. See MPEP § 806.05(h). In the instant case the products as claimed can be used in materially different processes of using the products, such as methods of the inventions of Groups IV-VI.

Art Unit: 1656

Inventions of Groups XVI-XVIII and Groups I-III are related as processes of making and products made. The inventions are distinct if either or both of the following can be shown: (1) that the processes as claimed can be used to make other, materially different, products or (2) that the products as claimed can be made by other, materially different processes (MPEP § 806.05(f)). In the instant case the processes as claimed can be used to make other, materially different products such as chemically- or fluorescently-labeled  $\alpha/\beta$  serine hydrolases, subtilisins, and chymotrypsins.

Inventions of Groups IV-XV are unrelated, one to another. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the different inventions are not disclosed as capable of use together and they have different modes of operation and different effects.

Inventions of Groups IV-XV are unrelated to the inventions of Groups XVI-XVIII. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the different inventions are not disclosed as capable of use together and they have different designs, different modes of operation, and different effects.

Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

- (a) the inventions have acquired a separate status in the art in view of their different classification;
- (b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;
- (c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);
- (d) the prior art applicable to one invention would not likely be applicable to another invention;
- (e) the inventions are likely to raise different non-prior art issues under 35 USC § 101 and/or 35 USC § 112, first paragraph.

**Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.**

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an

Art Unit: 1656

election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention.

If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 USC § 103(a) of the other invention.

A. Claims 1-20 of Group II are generic to the following disclosed patentably distinct species of cysteine-modified subtilisins, as evidenced by the recitation of claims 6, 8, 15 and 16:

1. A subtilisin modified by a replacement of a cysteine for an amino acid at an S<sub>1</sub> subsite position other than positions 156 or 166 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
2. A subtilisin modified by the replacement of a cysteine for an amino acid at an S<sub>1</sub> subsite position 156 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
3. A subtilisin modified by the replacement a cysteine for an amino acid at an S<sub>1</sub> subsite position 166 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
4. A subtilisin modified by a replacement of a cysteine for an amino acid at an S<sub>2</sub> subsite position other than a position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
5. A subtilisin modified by a replacement of a cysteine for an amino acid at an S<sub>2</sub> subsite position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
6. A subtilisin modified by a replacement of a cysteine for an amino acid at an S<sub>1</sub>' subsite position other than positions 217 or 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
7. A subtilisin modified by the replacement of a cysteine for an amino acid at an S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
8. A subtilisin modified by the replacement a cysteine for an amino acid at an S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
9. A subtilisin modified by replacements of cysteine for amino acids at both of S<sub>1</sub> subsite positions 156 and 166 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
10. A subtilisin modified by replacements of cysteine for an amino acid at S<sub>1</sub> subsite position 156 and S<sub>2</sub> subsite position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

Art Unit: 1656

11. A subtilisin modified by replacements of cysteine for an amino acid at S<sub>1</sub> subsite position 166 and S<sub>2</sub> subsite position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
12. A subtilisin modified by replacements of cysteine for amino acids at S<sub>2</sub> subsite position 62 and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
13. A subtilisin modified by replacements of cysteine for amino acids at S<sub>2</sub> subsite position 62 and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
14. A subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 156 and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
15. A subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 156 and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
16. A subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 166 and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
17. A subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 166 and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
18. A subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 156 and 166 and S<sub>2</sub> subsite position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
19. A subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub>' subsite positions 217 and 222 and S<sub>2</sub> subsite position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
20. A subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 156, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
21. A subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 166, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
22. A subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 156, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
23. A subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 166, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

Art Unit: 1656

24. A subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 156 and 166, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

25. A subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 156 and 166, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

26. A subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 156 and 166, and both S<sub>1</sub>' subsite positions 217 and 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

27. A subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite positions 156, S<sub>2</sub> subsite position 62, and both S<sub>1</sub>' subsite position 217 and 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

28. A subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 166, S<sub>2</sub> subsite position 62, and both S<sub>1</sub>' subsite positions 217 and 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

29. A subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 156 and 166, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

30. A subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 156 and 166, S<sub>2</sub> subsite position 62, and both S<sub>1</sub>' subsite positions 217 and 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

The species are independent or distinct because as disclosed the different species have mutually exclusive characteristics for each identified species since each position modified by a cysteine replacement may be covalently bonded to many further species of substituents, of which the substituents of claim 20 are but an exemplary subset. In addition, these species are not obvious variants of each other based on the current record.

Upon the election of an invention of Group I, Applicant is required under 35 USC § 121 to elect a single disclosed species from among the species listed in A, above, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 1-20 are generic.

B. Claims 21-30 of Group V are generic to the following disclosed patentably distinct species of methods of peptide bond formation utilizing cysteine-modified subtilisins:

1. A method utilizing a subtilisin modified by a replacement of a cysteine for an amino acid at an S<sub>1</sub> subsite position other than positions 156 or 166 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.



Art Unit: 1656

2. A method utilizing a subtilisin modified by the replacement of a cysteine for an amino acid at an S<sub>1</sub> subsite position 156 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
3. A method utilizing a subtilisin modified by the replacement a cysteine for an amino acid at an S<sub>1</sub> subsite position 166 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
4. A method utilizing a subtilisin modified by a replacement of a cysteine for an amino acid at an S<sub>2</sub> subsite position other than a position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
5. A method utilizing a subtilisin modified by a replacement of a cysteine for an amino acid at an S<sub>2</sub> subsite position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
6. A method utilizing a subtilisin modified by a replacement of a cysteine for an amino acid at an S<sub>1</sub>' subsite position other than positions 217 or 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
7. A method utilizing a subtilisin modified by the replacement of a cysteine for an amino acid at an S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
8. A method utilizing a subtilisin modified by the replacement a cysteine for an amino acid at an S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
9. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at both of S<sub>1</sub> subsite positions 156 and 166 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
10. A method utilizing a subtilisin modified by replacements of cysteine for an amino acid at S<sub>1</sub> subsite position 156 and S<sub>2</sub> subsite position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
11. A method utilizing a subtilisin modified by replacements of cysteine for an amino acid at S<sub>1</sub> subsite position 166 and S<sub>2</sub> subsite position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
12. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>2</sub> subsite position 62 and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
13. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>2</sub> subsite position 62 and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
14. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 156 and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
15. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 156 and S<sub>1</sub>' subsite position 222 as numbered by

Art Unit: 1656

correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

16. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 166 and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

17. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 166 and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

18. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 156 and 166 and S<sub>2</sub> subsite position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

19. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub>' subsite positions 217 and 222 and S<sub>2</sub> subsite position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

20. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 156, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

21. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 166, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

22. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 156, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

23. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 166, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

24. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 156, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

25. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 156 and 166, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

26. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 156 and 166, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

Art Unit: 1656

27. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 156 and 166, and both S<sub>1</sub>' subsite positions 217 and 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

28. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite positions 156, S<sub>2</sub> subsite position 62, and both S<sub>1</sub>' subsite position 217 and 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

29. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 166, S<sub>2</sub> subsite position 62, and both S<sub>1</sub>' subsite positions 217 and 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

30. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 156 and 166, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

The species are independent or distinct because as disclosed the different species have mutually exclusive characteristics for each identified species since each position modified by a cysteine replacement may be covalently bonded to many further species of substituents. In addition, these species are not obvious variants of each other based on the current record.

Upon the election of an invention of Group II, Applicant is required under 35 USC § 121 to elect a single disclosed method species from among the species listed in B, above, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 21-30 are generic.

C. Claims 31-37 of Group VIII are generic to the following disclosed patentably distinct species of methods of resolving compositions of racemic primary or secondary alcohols utilizing cysteine-modified subtilisins:

1. A method utilizing a subtilisin modified by a replacement of a cysteine for an amino acid at an S<sub>1</sub> subsite position other than positions 156 or 166 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

2. A method utilizing a subtilisin modified by the replacement of a cysteine for an amino acid at an S<sub>1</sub> subsite position 156 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

3. A method utilizing a subtilisin modified by the replacement a cysteine for an amino acid at an S<sub>1</sub> subsite position 166 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

4. A method utilizing a subtilisin modified by a replacement of a cysteine for an amino acid at an S<sub>2</sub> subsite position other than a position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

Art Unit: 1656

5. A method utilizing a subtilisin modified by a replacement of a cysteine for an amino acid at an S<sub>2</sub> subsite position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
6. A method utilizing a subtilisin modified by a replacement of a cysteine for an amino acid at an S<sub>1</sub>' subsite position other than positions 217 or 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
7. A method utilizing a subtilisin modified by the replacement of a cysteine for an amino acid at an S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
8. A method utilizing a subtilisin modified by the replacement a cysteine for an amino acid at an S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
9. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at both of S<sub>1</sub> subsite positions 156 and 166 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
10. A method utilizing a subtilisin modified by replacements of cysteine for an amino acid at S<sub>1</sub> subsite position 156 and S<sub>2</sub> subsite position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
11. A method utilizing a subtilisin modified by replacements of cysteine for an amino acid at S<sub>1</sub> subsite position 166 and S<sub>2</sub> subsite position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
12. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>2</sub> subsite position 62 and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
13. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>2</sub> subsite position 62 and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
14. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 156 and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
15. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 156 and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

Art Unit: 1656

16. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 166 and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
17. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 166 and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
18. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 156 and 166 and S<sub>2</sub> subsite position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
19. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub>' subsite positions 217 and 222 and S<sub>2</sub> subsite position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
20. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 156, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
21. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 166, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
22. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 156, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
23. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 166, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
24. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 156, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
25. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 156 and 166, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite

Art Unit: 1656

position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

26. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 156 and 166, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

27. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 156 and 166, and both S<sub>1</sub>' subsite positions 217 and 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

28. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite positions 156, S<sub>2</sub> subsite position 62, and both S<sub>1</sub>' subsite position 217 and 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

29. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 166, S<sub>2</sub> subsite position 62, and both S<sub>1</sub>' subsite positions 217 and 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

30. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 156 and 166, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

The species are independent or distinct because as disclosed the different species have mutually exclusive characteristics for each identified species since each position modified by a cysteine replacement may be covalently bonded to many further species of substituents. In addition, these species are not obvious variants of each other based on the current record.

Upon the election of an invention of Group III, Applicant is required under 35 USC § 121 to elect a single disclosed method species from among the species listed in C, above, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 31-37 are generic.

D. Claims 38-42 of Group XI are generic to the following disclosed patentably distinct species of methods of attaching a chiral moiety to a substrate utilizing cysteine-modified subtilisins:

1. A method utilizing a subtilisin modified by a replacement of a cysteine for an amino acid at an S<sub>1</sub> subsite position other than positions 156 or 166 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

Art Unit: 1656

2. A method utilizing a subtilisin modified by the replacement of a cysteine for an amino acid at an S<sub>1</sub> subsite position 156 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
3. A method utilizing a subtilisin modified by the replacement a cysteine for an amino acid at an S<sub>1</sub> subsite position 166 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
4. A method utilizing a subtilisin modified by a replacement of a cysteine for an amino acid at an S<sub>2</sub> subsite position other than a position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
5. A method utilizing a subtilisin modified by a replacement of a cysteine for an amino acid at an S<sub>2</sub> subsite position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
6. A method utilizing a subtilisin modified by a replacement of a cysteine for an amino acid at an S<sub>1</sub>' subsite position other than positions 217 or 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
7. A method utilizing a subtilisin modified by the replacement of a cysteine for an amino acid at an S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
8. A method utilizing a subtilisin modified by the replacement a cysteine for an amino acid at an S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
9. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at both of S<sub>1</sub> subsite positions 156 and 166 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
10. A method utilizing a subtilisin modified by replacements of cysteine for an amino acid at S<sub>1</sub> subsite position 156 and S<sub>2</sub> subsite position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
11. A method utilizing a subtilisin modified by replacements of cysteine for an amino acid at S<sub>1</sub> subsite position 166 and S<sub>2</sub> subsite position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
12. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>2</sub> subsite position 62 and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
13. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>2</sub> subsite position 62 and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
14. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 156 and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
15. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 156 and S<sub>1</sub>' subsite position 222 as numbered by

Art Unit: 1656

correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

16. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 166 and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

17. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 166 and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

18. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 156 and 166 and S<sub>2</sub> subsite position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

19. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub>' subsite positions 217 and 222 and S<sub>2</sub> subsite position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

20. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 156, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

21. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 166, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

22. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 156, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

23. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 166, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

24. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 156, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

25. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 156 and 166, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

26. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 156 and 166, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.



Art Unit: 1656

27. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 156 and 166, and both S<sub>1</sub>' subsite positions 217 and 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

28. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite positions 156, S<sub>2</sub> subsite position 62, and both S<sub>1</sub>' subsite position 217 and 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

29. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 166, S<sub>2</sub> subsite position 62, and both S<sub>1</sub>' subsite positions 217 and 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

30. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 156 and 166, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

The species are independent or distinct because as disclosed the different species have mutually exclusive characteristics for each identified species since each position modified by a cysteine replacement may be covalently bonded to many further species of substituents. In addition, these species are not obvious variants of each other based on the current record.

Upon the election of an invention of Group IV, Applicant is required under 35 USC § 121 to elect a single disclosed species from among the sets of species of D, above for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 38-42 are generic.

E. Claims 43-50 of Group XIV are generic to the following disclosed patentably distinct species of methods of lengthening a polypeptide by forming a peptide at the carboxyl terminus thereof utilizing cysteine-modified subtilisins:

1. A method utilizing a subtilisin modified by a replacement of a cysteine for an amino acid at an S<sub>1</sub> subsite position other than positions 156 or 166 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

2. A method utilizing a subtilisin modified by the replacement of a cysteine for an amino acid at an S<sub>1</sub> subsite position 156 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

3. A method utilizing a subtilisin modified by the replacement a cysteine for an amino acid at an S<sub>1</sub> subsite position 166 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

4. A method utilizing a subtilisin modified by a replacement of a cysteine for an amino acid at an S<sub>2</sub> subsite position other than a position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

Art Unit: 1656

5. A method utilizing a subtilisin modified by a replacement of a cysteine for an amino acid at an S<sub>2</sub> subsite position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
6. A method utilizing a subtilisin modified by a replacement of a cysteine for an amino acid at an S<sub>1</sub>' subsite position other than positions 217 or 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
7. A method utilizing a subtilisin modified by the replacement of a cysteine for an amino acid at an S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
8. A method utilizing a subtilisin modified by the replacement a cysteine for an amino acid at an S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
9. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at both of S<sub>1</sub> subsite positions 156 and 166 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
10. A method utilizing a subtilisin modified by replacements of cysteine for an amino acid at S<sub>1</sub> subsite position 156 and S<sub>2</sub> subsite position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
11. A method utilizing a subtilisin modified by replacements of cysteine for an amino acid at S<sub>1</sub> subsite position 166 and S<sub>2</sub> subsite position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
12. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>2</sub> subsite position 62 and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
13. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>2</sub> subsite position 62 and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
14. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 156 and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
15. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 156 and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
16. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 166 and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
17. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 166 and S<sub>1</sub>' subsite position 222 as numbered by

Art Unit: 1656

correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

18. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 156 and 166 and S<sub>2</sub> subsite position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

19. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub>' subsite positions 217 and 222 and S<sub>2</sub> subsite position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

20. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 156, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

21. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 166, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

22. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 156, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

23. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 166, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

24. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 156, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

25. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 156 and 166, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

26. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 156 and 166, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

27. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 156 and 166, and both S<sub>1</sub>' subsite positions 217 and 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

28. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite positions 156, S<sub>2</sub> subsite position 62, and both S<sub>1</sub>' subsite position 217 and 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

Art Unit: 1656

29. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 166, S<sub>2</sub> subsite position 62, and both S<sub>1</sub>' subsite positions 217 and 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

30. A method utilizing a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 156 and 166, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

The species are independent or distinct because as disclosed the different species have mutually exclusive characteristics for each identified species since each position modified by a cysteine replacement may be covalently bonded to many further species of substituents. In addition, these species are not obvious variants of each other based on the current record.

Upon the election of an invention of Group V, Applicant is required under 35 USC § 121 to elect a single disclosed species from among the sets of species of E, above, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 43-50 are generic.

E. Claims 51-62 of Group XVII are generic to the following disclosed patentably distinct species of methods of making cysteine-modified subtilisins:

1. A method that produces a subtilisin modified by a replacement of a cysteine for an amino acid at an S<sub>1</sub> subsite position other than positions 156 or 166 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
2. A method that produces a subtilisin modified by the replacement of a cysteine for an amino acid at an S<sub>1</sub> subsite position 156 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
3. A method that produces a subtilisin modified by the replacement a cysteine for an amino acid at an S<sub>1</sub> subsite position 166 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
4. A method that produces a subtilisin modified by a replacement of a cysteine for an amino acid at an S<sub>2</sub> subsite position other than a position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
5. A method that produces a subtilisin modified by a replacement of a cysteine for an amino acid at an S<sub>2</sub> subsite position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
6. A method that produces a subtilisin modified by a replacement of a cysteine for an amino acid at an S<sub>1</sub>' subsite position other than positions 217 or 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
7. A method that produces a subtilisin modified by the replacement of a cysteine for an amino acid at an S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

Art Unit: 1656

8. A method that produces a subtilisin modified by the replacement a cysteine for an amino acid at an S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
9. A method that produces a subtilisin modified by replacements of cysteine for amino acids at both of S<sub>1</sub> subsite positions 156 and 166 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
10. A method that produces a subtilisin modified by replacements of cysteine for an amino acid at S<sub>1</sub> subsite position 156 and S<sub>2</sub> subsite position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
11. A method that produces a subtilisin modified by replacements of cysteine for an amino acid at S<sub>1</sub> subsite position 166 and S<sub>2</sub> subsite position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
12. A method that produces a subtilisin modified by replacements of cysteine for amino acids at S<sub>2</sub> subsite position 62 and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
13. A method that produces a subtilisin modified by replacements of cysteine for amino acids at S<sub>2</sub> subsite position 62 and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
14. A method that produces a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 156 and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
15. A method that produces a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 156 and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
16. A method that produces a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 166 and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
17. A method that produces a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 166 and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
18. A method that produces a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 156 and 166 and S<sub>2</sub> subsite position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.
19. A method that produces a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub>' subsite positions 217 and 222 and S<sub>2</sub> subsite position 62 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

Art Unit: 1656

20. A method that produces a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 156, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

21. A method that produces a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 166, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

22. A method that produces a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 156, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

23. A method that produces a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 166, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

24. A method that produces a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite position 156, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

25. A method that produces a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 156 and 166, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 217 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

26. A method that produces a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 156 and 166, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

27. A method that produces a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 156 and 166, and both S<sub>1</sub>' subsite positions 217 and 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

28. A method that produces a subtilisin modified by replacements of cysteine for amino acids at S<sub>1</sub> subsite positions 156, S<sub>2</sub> subsite position 62, and both S<sub>1</sub>' subsite position 217 and 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

29. A method that produces a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 166, S<sub>2</sub> subsite position 62, and both S<sub>1</sub>' subsite positions 217 and 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

30. A method that produces a subtilisin modified by replacements of cysteine for amino acids at both S<sub>1</sub> subsite positions 156 and 166, S<sub>2</sub> subsite position 62, and S<sub>1</sub>' subsite position 222 as numbered by correspondence with positions in the amino acid sequence of the mature subtilisin BPN'.

The species are independent or distinct because as disclosed the different species have mutually exclusive characteristics for each identified species since each position modified by a

Art Unit: 1656

cysteine replacement may be covalently bonded to many further species of substituents. In addition, these species are not obvious variants of each other based on the current record.

Upon the election of an invention of Group VI, Applicant is required under 35 USC § 121 to elect a single disclosed species from among the sets of species of F, above, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 51-62 are generic.

There is an examination and search burden for these patentably distinct species in each of the sets A, B, C, D, and E, above due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 USC § 101 and/or 35 USC § 112, first paragraph.

**Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.**

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 USC § 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

#### *Notice of Requirements for Rejoinder*

The examiner has required restriction between product and process claims. Where applicant elects claims directed to a product, **and to a particular species thereof**, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim, **including the particular species thereof**, will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier.** Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

Art Unit: 1656

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. §§101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai*, *In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. §121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

#### *Inventorship*


Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

#### *Conclusion*

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 571.272.0933 and whose FAX number is 571.273.0933. The examiner can normally be reached Monday through Friday between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Primary Examiner, Dr. Kathleen Kerr Bragdon, can be reached at 571.272.0931. The official FAX number for all communications for the organization where this application or proceeding is assigned is 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.

/Nashed/  
Nashaat T. Nashed, Ph.D.  
Primary Examiner, Art Unit 1656

  
William W. Moore  
19 September 2007